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Benzodiazepines and memory

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1 Benzodiazepines possess anterograde amnesic properties, disrupting both short-term and long-term memory function.
2 The amount of amnesia is systematically related to dose effects and half-life differences among the benzodiazepines.
3 Memory deficits are found for episodic, semantic, and iconic memory function.
4 The deficits in long-term memory are probably the result of a disruption of consolidation of information in memory and not retrieval from memory. The disruption is produced by rapid sleep onset.
5 Thus the long-term amnesia is really a retrograde effect of sleep and not the anterograde effect of the drug.

Keywords benzodiazepines memory

Introduction

The rational and effective use of benzodiazepines in the symptomatic treatment of insomnia requires among other things a complete understanding of their side effects. One potentially important side effect of benzodiazepines is that of amnesia. Clinically two types of amnesia have been differentiated, retrograde and anterograde. Retrograde amnesia, that is memory loss for events prior to administration of drug, has not been observed with benzodiazepines. The amnesia which has been reported with benzodiazepines is anterograde, that is forgetting events occurring subsequent to administration of the drug.

Most of the initial evidence that benzodiazepines have anterograde amnesia properties came from reports of their use as presurgery medications. These studies used i.v. administration and many were anecdotal in nature (Greenblatt & Shader, 1974). There were few reports of amnesia when administered orally in use as hypnotics or anxiolytics. For that reason route of administration was thought to be a critical factor in the occurrence of the amnesia (Greenblatt & Shader, 1974). In addition, it was not clear whether benzodiazepines as a class possessed amnesic properties or whether amnesia was specific to those compounds typically used as presurgery medications. This led to our development of a methodology to evaluate the anterograde amnesic properties of benzodiazepines in use as hypnotics.

The purpose of this paper is to review the methodology we have developed for the study of amnesia, to discuss its reliability and sensitivity, and to relate the results from our studies to those from other laboratories using different methods. In addition we will discuss what we hypothesize as the mechanism producing the amnesia and the evidence supporting that hypothesis.

Methodology

Subjects report to the laboratory 1 h before their usual bedtime. Electrodes are attached at standard placements for the continuous recording of the EEG (C3 and Oz), EMG (submental), and EOG. Thirty minutes prior to lights out medication, either placebo or active drug administered in a double-blind manner, is given. Then subjects go to bed and sleep recordings are obtained.

Three hours after administration of the medication (2.5 h after lights out) subjects are awakened by calling their names over the intercom. Three hours was selected to ensure

that peak plasma levels of all standard hypnotics could be achieved. The wake up call is repeated until at least 15 s of a waking EEG accompanied by eye movements, elevated submental muscle tone, and a verbal response occur. Then the technician enters the room, turns on the lights, and questions the subject to verify wakefulness. The subject arises and is seated at a desk for the presentation of the memory tasks.

Four memory tasks, each containing four details, are presented to the subjects. The relevant details of each task are varied from night to night. Prior to the experiment each subject is familiarized with the format of the memory tasks in one practice session. The tasks are:

1. *Pill task*. Subjects ingest one to four small candy mints with a fruit flavoured drink. The four details of this task to be remembered are the flavour of the fruit drink, the colour of the mints, the number of mints ingested, and the colour of the bottle containing the mints. So as not to be confused with the real study medication, the mints are different in size, shape and colour. Further, prior to the start of the experiment, subjects are told that the mints taken during the awakening do not contain a medication and they sign an informed consent stating such.
2. *Dressing task*. Subjects put on and take off several articles of clothing provided to them by the technician. Details for recall are the colour of one of the articles, the sequence of dressing, and the name of two of the articles.
3. *Time task*. Subjects read a pre-set time on a cardboard clock face and then reset the clock to a new time. They are asked to recall the original time to which the clock was set, the colour of the clock face, the type of numeral on the clock face, and the time to which they reset the clock.
4. *Travel task*. The subject is given a recorded message regarding travel reservations for a hypothetical journey. The details which subjects are to recall are the destination of the trip, the name of the airline, the time of departure, and the flight number.

After completing these tasks in the order listed above the subjects are asked to recall the 16 relevant details of the four tasks. Recall is assessed with a 16 item questionnaire prompting for each detail (i.e. 'The colour of the pills was '). Completion of the memory tasks and the questionnaire takes 15 min. Then subjects return to bed with instructions to go back to sleep. In the morning after 5.5 additional hours in bed (total bedtime of 8 h), subjects are awakened. On arising a second memory questionnaire, identical to that administered the previous night, is completed.

Reliability and sensitivity

The reliability of these methods of assessing memory was evaluated using test-retest and split-half measures of reliability. Mean recall (total correct questionnaire responses) in the morning under placebo conditions was 14.1 on day 1 and 14.2 on day 2 and the correlation coefficient was $r = 0.85$ (Roth *et al.*, 1980). Split-half reliability was measured by calculating the correlation between odd and even questionnaire items across the two placebo days. This correlation was $r = 0.65$. Recall for each specific task was compared to that of the other three tasks to determine if any specific task was more or less difficult. None of the inter task comparisons produced any significant differences across the two placebo days.

While the order of the four tasks was the same on repeated administrations from night to night, the relevant details were varied night to night. This precluded any memory improvement across nights. In one study with four administrations of the tasks over a 7 day experimental protocol the mean number of items recalled never varied by more than 0.4 items in the placebo condition (Roehrs *et al.*, 1983). This indicates that these methods produce a highly stable measure of memory.

The sensitivity of these methods of assessing memory can be seen from the results of a study comparing different doses of the same benzodiazepine and benzodiazepines with different half-lives. In the dose effect study triazolam 0.50 mg produced significantly more recall errors than 0.25 mg triazolam (Roehrs *et al.*, 1983). Also, both triazolam doses produced significantly more amnesia than placebo. Thus with this methodology systematic dose effects could be detected. Regarding half-life, one of the characteristic results of repeated administration of a drug at intervals shorter than its half-life is a build-up of blood levels resulting in an increased clinical effect. Repeated nightly administration of 30 mg flurazepam (a long-acting compound) was compared to 0.25 and 0.50 mg triazolam (a short-acting compound) (Roehrs *et al.*, 1983). Morning recall after the first night of flurazepam was similar to triazolam 0.25 mg and significantly different than triazolam 0.50 mg. However, after 4 and 6 nights of flurazepam recall had declined and was similar to 0.50 mg triazolam and significantly different than 0.25 mg triazolam. Thus

our methods detected the differential effects of half-life.

External validity

Rather than choosing one of the many commonly employed tests of memory, we tried to develop a set of tasks with direct clinical relevance. The tasks were chosen to mimic real life situations which might be encountered by patients during a night-time awakening after having used a benzodiazepine at bedtime. For example, patients using hypnotics sometimes awaken during the night and take additional pills. For proper medical care it would be important that the patient be able to recall in the morning the specifics of the awakening (number and type of additional pills). Or again, the accurate recall in the morning of a telephone message received during a night-time awakening may be important to a patient. This methodology of assessing memory impairments associated with benzodiazepines appears to have high face validity and results would seem to be generalizable to real life.

Results using these methods also correlate well with results from other studies using other measures of memory. Flunitrazepam and secobarbitone produced amnesia for tasks presented during a night-time awakening (Bixler *et al.*, 1979). These tasks, similar to those we use, included writing a cheque, describing a familiar topic, listing events occurring the past day, and performing a series of commands. Similarly, amnesia for verbal material, typically word lists or paired associates, have been found following benzodiazepines, including triazolam, flunitrazepam, lorazepam, diazepam, and flurazepam (Spinweber & Johnson, 1982; Scharf *et al.*, 1983; Brown *et al.*, 1982; Hill *et al.*, 1982). Finally, memory for pictures is impaired with diazepam, lorazepam and midazolam (Dundee & Wilson, 1980; McKay & Dundee, 1980; Flinn *et al.*, 1975).

Thus, amnesia is found regardless of the type of memory studied, whether it is primarily episodic (i.e. memory for events such as cheque writing or message taking), semantic, or iconic.

Theoretical validity

According to an information processing model memory is a multistage process involving the encoding, storage, and retrieval of information. Typically most models include a sensory memory, a short-term and a long-term memory. Information enters through sense organs into a sensory register where in several milliseconds attentional and encoding processes occur. The attended information enters a limited capacity short-term memory, the duration of which ranges from seconds to minutes. Then that information is either forgotten or may be transferred to a long-term memory where it is stored through a consolidation process for later retrieval. This consolidation process takes some unspecified period of time before a relatively permanent long-term memory trace is established.

A number of studies have shown various benzodiazepines disrupt short-term memory (Adams, 1974; Brown *et al.*, 1982; Hill *et al.*, 1982; Peck *et al.*, 1977; Scharf *et al.*, 1983; Spinweber & Johnson). Such studies involve the presentation of stimulus materials requiring a minute or less to complete which is then followed by an immediate test of recall. Short-term memory for series of digits (6–9 digits long) or short lists of words (16 words or less) is disturbed anywhere from 1.5 h to 20 h after drug administration, depending on the half-life of the drug (Adams, 1974; Spinweber & Johnson, 982). In our initial study immediate recall, although by most definitions not short-term memory, also was disturbed (Roth *et al.*, 1980). Remember, completion of the four memory tasks took 15 min, so the retention interval for the first task was at least 10 min. However, the fact that immediate memory in our task, like the short-term tasks, is disrupted by benzodiazepines was not too surprising. Hypnotics produced a general depression of waking CNS function as well as producing sleep. Of greater interest was the further memory loss from the immediate recall to the morning recall test. By using cued recall rather than free recall as in the first study (Roth *et al.*, 1980), we were able in subsequent studies to ameliorate some of the immediate loss in order to focus on long-term memory deficits.

Long-term memory deficits (morning recall in our methodology) could be the result of failure of memory consolidation at night or failure of memory retrieval in the morning. In the first study we found that morning recall was correlated ($r = 0.74$) with the latency to fall back asleep after the night-time awakening (Roth *et al.*, 1980). Figure 1 illustrates the correlation. This suggests that failure of memory consolidation due to rapid sleep onset was the most likely explanation for the memory loss associated with these drugs. In other words sleep was interfering with memory consolidation. To test the hypothesis, sleep onset was postponed for 15 min after the completion of the memory tasks and the immediate memory

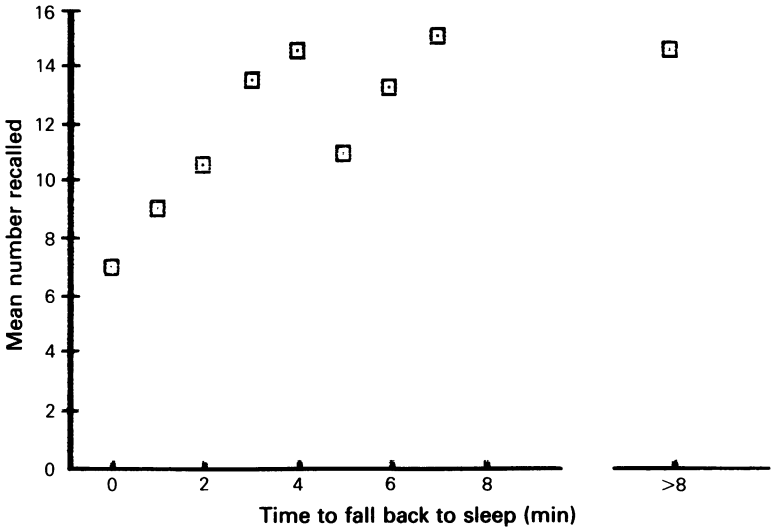

Figure 1 Relation of recall to sleep latency.

testing (Roehrs *et al.*, 1983). The results showed that maintenance of wakefulness did reduce amnesia in the morning even after taking drug at bedtime. In addition, if rapid sleep onset was interfering with memory consolidation, then any drug which produces rapid sleep onset should have amnesic effects. The same study compared a benzodiazepine to a barbiturate with similar potency and kinetics and both produced similar amounts of amnesia (Roehrs *et al.*, 1983). Finally, in a recent study the correlation between sleep latency after a night-time awakening and recall of the memory tasks in the morning was $r = 0.86$ (Roehrs *et al.*, 1984).

Results from several nonpharmacological studies suggest that sleep can interfere with the consolidation of memory traces in long-term memory. In one study words presented just before (less than 5 min) the onset of sleep were forgotten after 10 min of sleep, but not after only 30 s or sleep (Guilleminault & Dement, 1977). Yet, and this is the crucial point, words presented 5 to 10 min before sleep onset could be remembered whether retrieval was tested 30 s or 10 min after sleep onset. Two other studies found that subjects awakened several times each night were more likely to remember a word shown to them incidentally (a slide projector on the wall at the foot of the bed) if they spontaneously remained awake for a period of time than if they fell back to sleep quickly (Goodenough *et al.*, 1971; Portnoff *et al.*, 1966).

In summary, the data seem to indicate that some of the amnesia associated with benzodiazepines is due to a disruption of the consolidation of information in long-term memory by sleep. Thus, as regards any long-term amnesia associated with benzodiazepines, we are really then measuring the retrograde effects of sleep and probably not the anterograde effects of benzodiazepines.

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